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Delayed Versus Early Umbilical Cord Clamping

Bracha Yaffa Sachs
Touro College

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ABSTRACT

Immediate cord clamping is a part of the active management of the third stage of labor. Active management is standard birth protocol because it significantly reduces the risk of maternal postpartum hemorrhaging. However, since recent evidence advocates delayed cord clamping, various medical practitioners and health organizations would like to incorporate delayed cord clamping in place of immediate cord clamping as a part of standard birth protocol. Proposed benefits include a serious decline in the prevalence of anemia, especially, in countries where anemia is endemic, as well as a decrease in the risk of intraventricular hemorrhage and late onset sepsis. Although these advantages are significant and very important, there are concerns associated with increased risks such as neonatal jaundice, polycythemia, and maternal postpartum hemorrhage.

In order to come to a conclusion, researchers and professionals must calculate the risks versus the benefits of delayed cord clamping based on numerous experiments and randomized controlled trials. Based on the latest research data in the postnatal health arena, delayed cord clamping is a beneficial and risk free technique to manage the umbilical cord for the first few minutes in healthy neonates.

INTRODUCTION

The vein and two arteries within the umbilical cord provide the necessary nutrition for the fetus and dispose of its wastes. The umbilical vein brings oxygenated blood to the fetus, and the two umbilical arteries carry deoxygenated blood away from the fetus (Tortora and Grabowski 2003a). Without the umbilical cord connection, a fetus cannot survive in its mother's uterus. Immediately after an infant is born, the decline of the infant's intrathoracic pressure will draw blood from the umbilical cord into the lung. Therefore, as long as the umbilical cord remains unclamped, blood passes through to the infant at 19 ml/kg of the infant's birth weight, increasing the neonatal blood volume (Weeks 2007) (See Figure 1). Upon birth, active management is generally implemented. Active management is standard birth protocol, intended to significantly reduce the risk of maternal postpartum hemorrhaging. Included in active management are controlled cord traction, immediate clamping and drainage of the umbilical cord, and the administration of uterotonic agents. The standard practice is to tie and cut the umbilical cord within the first 15 seconds of birth, a process known as immediate or early cord clamping (ICC or ECC, respectively) (Eichenbaum-Pikser and Zasloff 2009). However, a growing body of evidence indicates that it would be beneficial to delay this clamping, a procedure known as delayed cord clamping (DCC). Is the evidence displaying potential benefits of delayed cord clamping substantial enough that mothers should delay the clamping of the cord to maximize the benefits that their children receive?

Bracha Yaffa Sachs, B.S. '12, majored in Biology. She is currently attending the Physician Assistant program at Pace University-Lenox Hill Hospital.

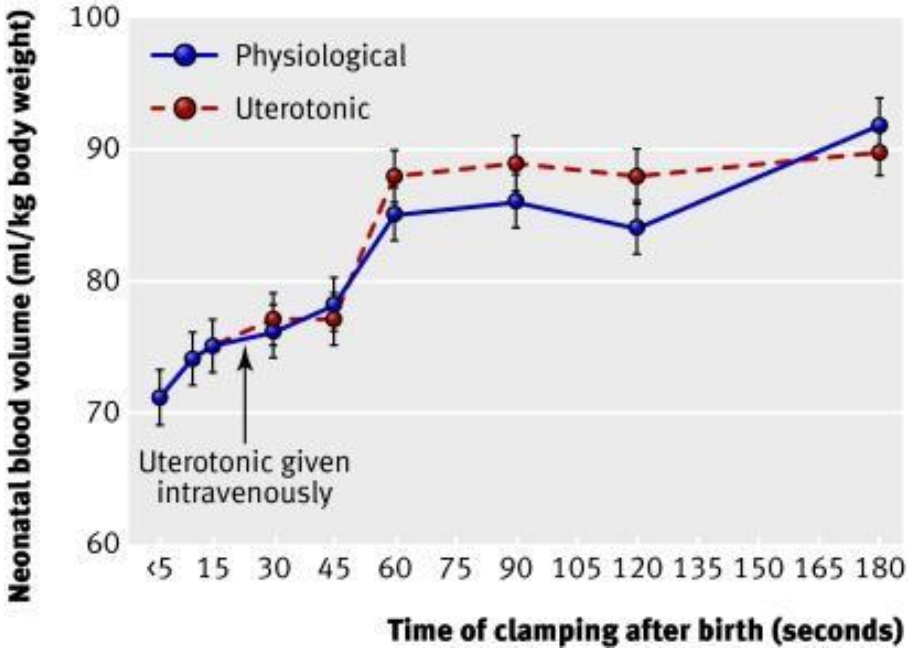

Figure 1: Changes in the neonatal blood volume with increasing delay of cord clamping, with and without the use of a uterotonic. Source: Weeks 2007

TIMING OF CORD CLAMPING AND INFANT POSITIONING

While the timing of immediate cord clamping in full term, preterm, and cesarean section born infants, ranges from clamping of the cord immediately after the baby is delivered up until 30 seconds post birth, the timing is not as defined in delayed cord clamping. Table 1 displays a range of times referred to in the literature as DCC.

Author, Year	Study Population	Cord Management	Statistically Significant Results	Recommendations
Strauss et al. 2008	Partially blind randomized controlled trial, < 36 wks EGA; early, n = 60; delayed, n = 45	Early = within 15 sec; delayed = 1 min	Circulating RBC vol/mass increased and Hct values were higher after delayed clamping	1 min delay in infants 30–36 wks EGA who do not need resuscitation
Hutton and Hassan 2007	15 randomized controlled trials, full-term infants	Early = immediately after birth; delayed = minimum of 2 min	Improved hematologic status over 2–6 mos with delayed clamping	Minimum of 2-min delay
McDonald and Middleton 2008	11 randomized controlled trials, full-term infants	Early = within 60 sec; delayed = > 1 min after birth or when cord pulsation ceased	No difference in rates of PPH, increase in neonatal Hgb/Hct; increase in jaundice	A more "liberal" approach to delaying clamping in healthy term infants

Jahazi et al. 2008	Healthy, full-term, vaginally born neonates; delayed, n = 34; early, n = 30	Early = 30 sec; delayed = 3 min	No increase in Hct noted; significantly increased ENBV	Potential benefit should be considered by providers
Utlee et al. 2007	randomized controlled trial, 34–37 wks EGA; early, n = 19; late, n = 18	Early = < 30 sec; late = > 180 sec	Delayed groups had higher Hgb levels at 1 hr postpartum and 10 wks old; no difference in the ferritin levels at 10 wks	Immediate cord clamping should be discouraged
Van Rheenen et al. 2007	Delayed, n = 46; control, n = 45	Awaited cessation of pulse, mean clamping time 305 sec (control mean clamping time, 15 sec)	Increase in PCV, increased Hgb at 4 mos	3-min delay
Cernadas et al. 2006	Early, n = 90; delayed 1, n = 90; delayed 2, n = 92	Early = within 15 sec; delayed 1 = 1-min delay; delayed 2 = 3-min delay	Hct at 6 hrs highest in delayed cord clamping, lowest in early; increase in anemia at 6 hrs and 24–48 hrs in early	Delay of at least 1 min
Van Rheenen and Brabin 2006	Four randomized controlled trials	Immediate = within 20 sec; delayed = 30 sec to 2 min	Decreased anemia up to 4 mos, higher iron levels up to 6 mos	Delay of at least 3 min
Rabe and Diaz-Rossello 2004	Seven randomized controlled trials	Early = within 30 sec; delayed = 30–120 sec	Decreased IVH, fewer blood transfusions	Delay of 30–120 sec

EGA= estimated gestational age; ENBV= estimated neonatal blood volume; Hct= hematocrit; Hgb= hemoglobin; IVH= intraventricular hemorrhage; PCV= packed cell volume; PPH= postpartum hemorrhage; RBC= red blood cell; RCT= randomized controlled trial.

Table 1: Variation in the definition of delayed cord clamping. Source: Eichenbaum- Pikser and Zasloff 2009

In DCC of a full term, healthy neonate, most doctors will wait until the cord ceases pulsating before clamping it (Kent 2010). Pulse cessation can either be defined as the complete

absence of a pulse, or as the presence of only a weak pulse. Van Rheenen et al. (2007) found that, on average, cord pulsation ceased completely 305 seconds after birth. Some doctors and midwives, however, consider DCC as clamping of the cord at any point after 30 seconds from birth (Eichenbaum- Pikser and Zasloff 2009). In DCC of preterm infants, the variance tends to be smaller, with trials reporting a clamping time of 30 seconds to one minute (Mercer et al. 2006; Strauss et al. 2008).

To maximize the volume of transfused blood, the neonate should be held about 10 to 15 inches below the site of delivery, and no unnecessary pressure should be placed on the cord (Mercer et al. 2006).

Benefits of Delayed Cord Clamping

Improved Hematocrit Levels, Decreased Iron Deficiency, and Prevalence of Anemia

Iron deficiency and iron deficiency anemia are endemic in underdeveloped countries and poor populations. Since the brain requires iron for neuron myelination, dendritic growth, neurotransmission, and in neural and glial energy metabolism, iron deficiency in infants is linked to neurodevelopmental delays (Lewis 2011). Some of the detrimental effects that happen as a result of iron deficiency are irreversible, even after iron treatment. Delaying umbilical cord clamping after birth increases the volume of blood transfusion and results in a decrease in infant iron deficiency (Mercer and Erickson-Owens 2006).

A large, randomized study conducted in Mexico City found that infants in the DCC group had less iron deficiency and iron deficiency anemia than infants in the ICC group. Additionally, infants in the DCC group had a higher mean corpuscular volume, higher levels of body and stored iron, higher levels of ferritin, and a lower ratio of transferrin receptor to ferritin than those in the ICC group (Chaparro et al. 2006) (Figures 2 and 3).

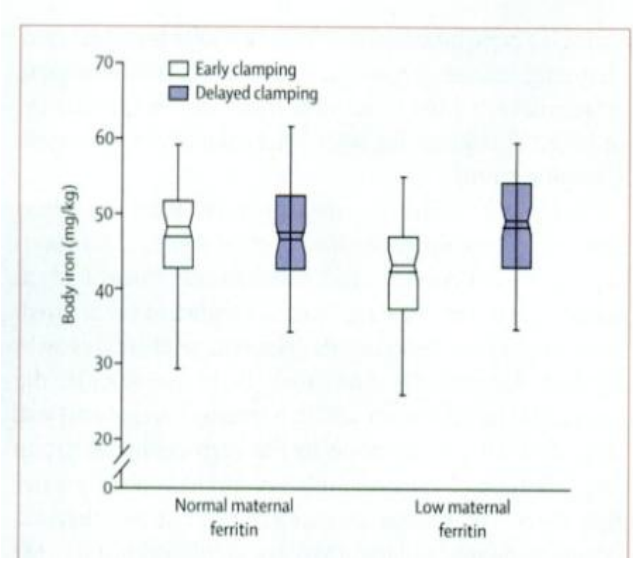

Figure 2: Box-and-whisker plot of two-way interaction effect of treatment group and maternal ferritin on infant body iron (mg/kg) at 6 months of age. Boxes represent the inter-quartile range (25th to 75th percentile), and whiskers indicate the 5th and 95th percentiles for the unadjusted data. The notch in each box represents Cl about the median, represented by horizontal line at the middle of the notch. Additional horizontal line represents the mean of each subgroup. Treatment difference (early clamping vs. delayed clamping, adjusted for maternal ferritin and employment) in body iron in infants born to mothers with normal ferritin concentrations was -0.8 mg/kg (95% Cl- 5.0 to 3.4 mg/kg). Treatment difference (adjusted) in body iron in infants born to mothers with low ferritin concentrations was -6.5 mg/kg (-10.2 to -2.8 mg/kg). Low maternal ferritin is <12 μg/L; normal maternal ferritin is ≥ 12 μg/L. p=0.008 for interaction term. Source: Chaparro et al. 2006

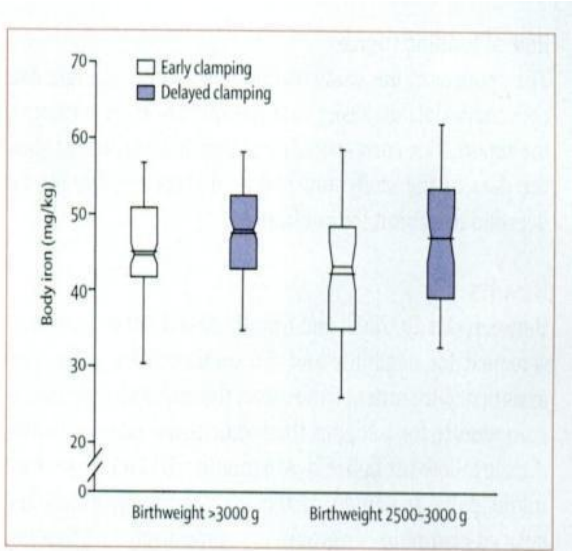

Figure 3: Two-way interaction effect of treatment group and infant birth weight on infant body iron (mg/kg) at 6 months of age. Treatment difference (early clamping vs. delayed clamping, adjusted for maternal ferritin and employment) in body iron in infants born with birth weight more than 3000 g was -3.5 mg/kg (95% Cl- 5.9 to 0.9 mg/kg). Treatment difference (adjusted) in body iron in infants with birth weight between 2500 g and 3000 g was 7.1 mg/kg (-11.9 to -2.4 mg/kg). p=0.04 for interaction term. Source: Chaparro et al. 2006

DCC can also reduce anemia in preterm infants. A review analysis of ten randomized trials, with a total of 454 premature infants within 37 weeks gestational age, found that infants with DCC had significantly higher hematocrit levels and less transfusions for anemia than those with ICC (Rabe et al. 2008) (See Table 2). However, the groups in these studies were relatively small, containing only between 19 to 86 participants.

Study	ECC n/N	LCC n/N	Relative risk (fixed-effects model)
Outcome: transfused for anaemia			
Kinmond et al. 1993	7/13	1/13	7.00 (1.00, 49.16)
McDonnell et al. 1997	6/23	4/23	1.50 (0.49, 4.62)
Rabe et al. 2000	16/20	9/19	1.69 (1.00, 2.85)
Total	56	55	2.01 (1.24, 3.27)
Total events: 29 early, 14 delayed			
Test for heterogeneity: x^2=2.26, df=2 (p=0.32), I^2=11.5%. Test for overall effect: Z=2.81 (p=0.005).			

Study	N	ECC	N	LCC	WMD (fixed)
Outcome: transfused for anaemia					
Kinmond et al. 1993	13	1.91 ± 1.62	13	0.46 ± 0.66	1.45 (0.50, 2.40)
Rabe et al. 2000	20	2.40 ± 1.95	19	1.20 ± 1.60	1.20 (0.08, 2.32)
Oh et al. 2002	17	4.00 ± 4.00	16	3.60 ± 3.80	0.40 (-2.26, 3.06)
Mercer et al. 2006	36	2.47 ± 3.70	36	1.94 ± 3.10	0.53 (-1.05, 2.11)
Total	86		84		1.16 (0.52, 1.80)
Total events: none recorded					
Test for heterogeneity: x^2=1.29, df=3 (p=0.73), I^2=0%. Test for overall effect: Z=3.55 (p=0.0004).					

Table 2: Figures in parentheses are 95% CI. ECC= Early cord clamping; LCC- late cord clamping; WMD= weighted mean difference; df= degrees of freedom. Source: Rabe et al. 2008

A slightly larger trial, consisting of 105 preterm infants, also found that infants in the DCC group had higher hematocrit levels, red blood cell volume, and iron levels. Infants in this study had a gestational age of 36 weeks or less (Strauss et al. 2008).

DCC can also benefit healthy, full term infants born in developed countries. A study of 400 mother-infant pairs in Sweden found higher ferritin concentration and total body iron in the DCC group at four months. The DCC group also had lower numbers of anemic infants at two days from birth (Andersson et al. 2011).

According to one research group, the higher birth weight of 96 grams on average in infants with delayed cord clamping denotes a higher placental transfusion in the DCC group. Additionally, in two-day-old infants, the placenta retained less blood and raised levels of hemoglobin and hematocrit (Andersson et al. 2011). However, perhaps the increased birth weight is a result of natural factors. Also, although a possible explanation accounting for the lower hemoglobin concentration in the DCC is proposed, there is no scientific reason given. On one hand, the trial proves the effectiveness of increasing iron stores and decreasing iron deficiency at four months in infants born in countries that do not have an endemic iron deficiency anemia. Yet, the research confirms the conclusion only in full term healthy infants, and not in premature births or in births from complicated pregnancies in the same setting.

DECREASED RISK OF INTRAVENTRICULAR HEMORRHAGE

Premature infants are at a higher risk for intraventricular hemorrhage (IVH) than full term infants, with infants born within 28 weeks gestational age having the greatest risk (Kling 2010).

A study by Mercer et al. (2006) found that infants with ICC had a higher risk of IVH than those with DCC. In the ICC group, IVH affected some 42 % of males and 29 % of females, whereas IVH affected only 9 % and 23 % respectively, in the DCC group. A recent follow-up study found similar results, with infants in the DCC group showing a 50 % reduction in IVH (Mercer et al. 2010). This study also tested for neurodevelopmental outcomes of DCC and showed that as a result of lower rates of intraventricular hemorrhage, the infants had better motor performance at seven months. Although the positive motor performance is dominant in male infants (Mercer et al. 2010), a reason for this particular outcome is unknown. The improvement of the neurodevelopmental status in male infants resulting from lower rates of intraventricular hemorrhage may be due to the fact that intraventricular hemorrhage has shown to be more widespread in the males with ICC.

Table 3 below reviews a number of studies reflecting a lower rate of IVH in infants with DCC.

Study	ECC n/N	LCC n/N	Relative risk (fixed-effects model)
Outcome: intraventricular haemorrhage			
Hofmeyr et al. 1993	11/46	8/40	1.20 (0.53, 2.68)
Hofmeyr et al. 1988	10/13	8/23	2.21 (1.17, 4.17)
McDonnell et al. 1997	1/16	0/15	2.82 (0.12, 64.39)
Rabe et al. 2000	3/20	1/19	2.85 (0.32, 25.07)
Oh et al. 2002	4/17	2/16	1.88 (0.40, 8.90)
Mercer et al. 2003	5/16	3/16	1.67 (.48, 5.83)
Mercer et al. 2006	13/36	5/36	2.60 (1.03, 6.54)
Total	164	165	1.90 (1.27, 3.84)
Total events: 47 early, 27 delayed			
Test for heterogeneity: x^2=2.17, df=6 (p=0.90), I^2=0%. Test for overall effect: Z=3.13 (p=0.002).			

Table 3: ECC= early cord clamping, LCC= late cord clamping, df= degrees of freedom. Source: Rabe et al. 2008

Several studies propose possible mechanisms for this decrease in occurrences of intraventricular hemorrhage. Dr. Backes suggests that the results are due to an increase in progenitor cell percentages within 48 hours of birth. However, this increase is not significant anymore by the time the infants are 30 days old (Kling 2010). Alternatively, Rabe et al. (2008) suggest that this decrease may be a reflection of improved cardiovascular stability that results from the delayed clamping. However, none of these explanations have been confirmed.

Strauss et al. (2008) found no significant decrease in intraventricular hemorrhage incidence in DCC v. ICC infants. However, the Society of Obstetricians and Gynecologists of Canada says that DCC in prematurely born infants reduces occurrences of intraventricular hemorrhage (Gordon 2010). Strauss et al. know that the outcome of their trial does not agree with previous outcomes and have suggested that the neonates in their trial were at least 30 weeks gestational age whereas those in other trials were generally under 30 weeks. However, the Society of Obstetricians and Gynecologists of Canada says that DCC significantly reduces intraventricular hemorrhage incidence in infants born at less than 37 weeks gestational age (Gordon 2010).

DECREASED RISK OF LATE ONSET SEPSIS

Decreases in the incidence of late onset sepsis (LOS) have been recently discovered as another potentially important outcome of DCC. Late onset sepsis is the probable cause behind infection and inflammation of infants born prematurely (Rabe et al. 2008).

In one study, while 22% of infants in the ICC group tested positive for LOS, only 3% of the DCC group tested positive. As an interesting aside, a higher percentage of late onset sepsis occurred in the more prematurely born infants. Of the eight infants from the ICC group and one from the DCC group diagnosed with LOS, six of them were born 24 to 27 weeks gestational age, and the other three were born 28 to 31 weeks gestational age. Interestingly, infants with sepsis had lower initial hematocrit levels, even when controlled for gestational age (Mercer et al. 2006).

In a more recent study, the results were almost identical to the previously mentioned study, with 21% of infants in the immediate cord clamping group and 3% of infants in the delayed cord clamping group testing positive for late onset sepsis (Mercer et al. 2010).

As seen with reduced incidence of intraventricular hemorrhage, gender comparisons indicate that with DCC, male infants have a greater reduction in late onset sepsis than female infants. In one experiment, six males and two females in the ICC group acquired LOS, while in the DCC group the number of infants with late onset sepsis was zero and one respectively (Mercer et al. 2006). Another trial records the same trend but does not give detailed data (Mercer et al. 2010). Although a clinically plausible explanation for this trend has not yet been proposed, it may be because late onset sepsis, like IVH, is more prevalent in male infants.

Babies born via a caesarean section would also greatly benefit from delayed cord clamping; only their precarious state generally requires earlier intervention. Nevertheless, a delay of at least one minute should be attempted (Weeks 2007). The same applies to full term or preterm babies requiring special care and support prior to umbilical cord pulse cessation (Eichenbaum- Pikser and Zasloff 2009).

Risks of Delayed Cord Clamping

Increased Risk of Neonatal Jaundice, Resulting in an Increased Phototherapy Treatment

Delayed cord clamping is often assumed to be liable for an increase in the incidence of neonatal jaundice (Eichenbaum-Pikser and Zaloff 2009). In Strauss et al. (2008) randomized trial, a significantly higher percentage of infants in the early cord clamping group required phototherapy to treat neonatal jaundice. However, there were no differences in the serum bilirubin levels, the age which the phototherapy treatment began, and the length or intensity of the treatment between the two groups. Another experiment indeed found higher bilirubin levels in DCC infants, but the levels generally did not exceed the phototherapy threshold, and the infants did not require exchange transfusion. The number of incidences where treatment was required did not differ significantly between the two groups (van Rheenen and Brabin 2006). In Chapparo et al. (2006) study of normal weight, full term Mexican infants, there was no difference between the two groups in the number of infants diagnosed with neonatal jaundice. In a study of healthy Swedish infants, only one infant in the DCC group required phototherapy for jaundice, as opposed to two infants in the ICC group. According to the Cochrane review (a collection of databases in medicine and other healthcare specialties), the fear of increased risk in neonatal jaundice relies on unpublished data (Andersson et al. 2011), and there is no evidence validating a relationship between DCC and neonatal jaundice (Strauss et al. 2008).

Increased Risk of Polycythemia

Polycythemia is diagnosed in neonates if they display venous blood hematocrit levels greater than 65% (Tortora and Grabowski 2003b). However, because the red blood cell volume from a peripheral vein is usually higher than other veins, some doctors may use 70% venous blood hematocrit as their cutoff mark (Chaparro et al. 2006). Concerns have been expressed that polycythemia might be a potential adverse effect of DCC (Andersson et al. 2011). In fact, according to Basile and Southgate (2004), delayed cord clamping is said to be the most common cause of polycythemia in full term healthy neonates since it results in higher levels of hematocrit.

However, studies on full term, healthy infants do not support this concern and conclude that polycythemia is not a risk of delayed cord clamping. In the study of Mexican infants by Chapparo et al. (2006), none of the infants presented with hematocrit levels greater than 70%. Although there were two infants in the DCC group whose hematocrit levels were slightly above

65%, they were not diagnosed with polycythemia. In the abovementioned Swedish study as well, none of the infants were diagnosed with polycythemia (Andersson et al. 2011).

Similar results were obtained from trials done on preterm and very low birth weight infants. In Strauss et al. (2008) study of preterm infants, although each time the hematocrit levels were assessed, the levels displayed in infants from the DCC group were significantly higher than those of the ICC group, they were always below 65% (Table 4). Like the full term healthy infants, none of the preterm infants were diagnosed with polycythemia.

	Day 0-1		**Day 7**		**Day 14**		**Day 21**		**Day 28**	
Clamping time	**Hct**	**PLT**	**Hct**	**PLT**	**Hct**	**PLT**	**Hct**	**PLT**	**Hct**	**PLT**
Immediate (n = 55)	53 ± 1.1	248 ± 17	47 ± 0.9	292 ± 28	41 ± 0.07	375 ± 33	36 ± 0.7	456 ± 36	31 ± 0.6	434 ± 37
Delayed (n = 41)	56 ± 1.3	241 ± 54	52 ± 1.0	334 ± 45	46 ± 0.8	365 ± 60	41 ± 0.9	401 ± 56	35 ± 0.8	469 ± 103
	$p = 0.188$		$p = 0.005$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	

Table 4: Hct= Hematocrit, PLT=platelet. Source: Strauss et al. 2008

Some experiments, however, do show DCC infants exceeding hematocrit thresholds. In a trial analysis conducted by Van Rheenen and Brabin (2004, quoted in Mercer et al. 2007), three infants in the DCC group were diagnosed with polycythemia. A similiar analysis conducted by Hutton and Hassan (2007, quoted in Eichenbaum-Pikser and Zaloff 2009) displays some infants with polycythemia at 7, 24, and 48 hours after birth, with a greater risk for DCC infants. However, in both cases, all of the diagnosed infants had asymptomatic polycythemia. Additionally, in a double blind randomized controlled trial by Jahazi et al. (2008, quoted in Eichenbaum-Pikser and Zaloff 2009), infants in both groups presented with polycythemia at two hours after birth, with no significant differences between the two groups.

INCREASE RISK OF MATERNAL POSTPARTUM HEMORRHAGE

Active management, versus expectant management, of the third stage of labor has been proven to decrease maternal postpartum hemorrhaging (PPH) (Miller et al. 2004). Included in active management of the third stage of labor are controlled cord traction, immediate clamping and drainage of the umbilical cord, and the administration of one or two uterotonic agents, e.g. oxytocin (Chelmow 2008). Expectant management is the delivery of the placenta via maternal effort, waiting for cessation of the cord pulse to clamp it, and refraining from administering uterotonic agents (Rogers et al. 1998). Chaparro et al. (2006) report that there is no evidence proving that ICC alone decreases the risks of maternal hemorrhage. They suggest that perhaps it is the combination of all the components of active management, including ICC, which decreases the risk of postpartum hemorrhage. Their study, however, suffered from an inability to properly measure maternal blood loss and can, therefore, be considered inconclusive.

Another study on the effects of delayed cord clamping on maternal postpartum hemorrhage showed no increase in hemorrhage with DCC. In this study, women were given either a simplified package of active management from which ICC was omitted, or a full package

of active management including ICC. The women who received the simplified package showed no substantial increase in maternal postpartum hemorrhage (Garcia 2012a). Dr. David Hutchon says that ICC is an unproven intervention for decreasing postpartum hemorrhaging (Gordon 2010). Andrew Weeks (2007) assumes that ICC was not intentionally added to the active management, since there is no evidence of it playing any role in reducing postpartum hemorrhage by itself or together with the other components of active management. Rather, Weeks assumes, the sole reason for the inclusion of ICC is most likely due to its having been included into standard birth protocol. The World Health Organization recommends the administration of oxytocin as well as controlled cord traction and suggests delaying the clamping and cutting of the cord until a healthcare worker is prepared to apply cord traction (Garcia 2012b).

CONCLUSION

Much research has been done concerning delayed cord clamping in the full term, preterm, and cesarean section neonates. In all the experiments, while none of the outcomes confirm the possible risks of DCC, substantial evidence verifies its benefits. Therefore, not only should mothers be educated about the concept of DCC, but DCC should also be integrated into standard birth protocol in healthy infants.

With regard to infants born with major health issues, further research is still required to determine whether or not the DCC method is safe enough to be incorporated in standard birth protocol.

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